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Asymmetric Synthesis of α-Fluoro Ketones using α-Fluoro Oxazolidinone Carboximides

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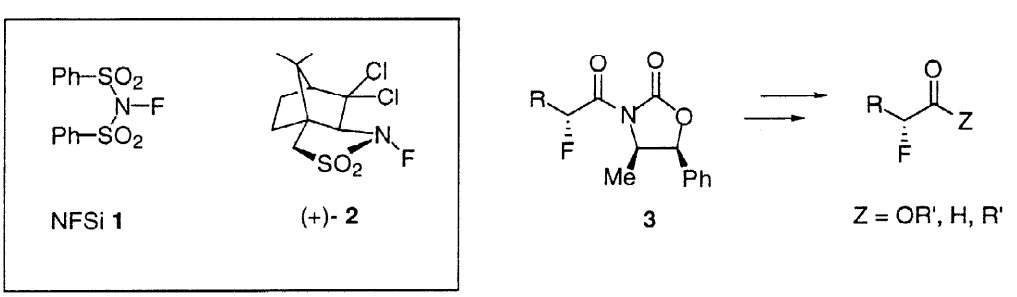
Summary: *Addition of Grignard reagents to enantiopure α-fluoro N-methoxy-N-methylamides* ***5*** *affords α-fluoro ketones (R)-6 in >96% ee.*

The strategic introduction of fluorine into bioactive molecules is used to enhance biological activity, and study mechanisms of action.[1,2] In this context increasing attention is being directed towards the development of methodologies for the asymmetric synthesis of fluoro organic molecules where fluorine is attached to a stereogenic carbon.[3] This is in recognition of the importance of chirality in biologically and pharmacologically active molecules and its application to drug design, agro chemicals and the synthesis of new materials. One approach to the synthesis of chiral fluoro organic molecules is to construct building blocks, such as α-fluoro carbonyl compounds [RCH(F)C(O)Z], that can then be employed in the preparation of more complex derivatives (Scheme 1).[4] Enantiomerically enriched α-fluoro carbonyl derivatives have been prepared by enzyme catalyzed kinetic resolution of α-fluoro esters,[5] fluorodeamination of α-amino acids[6a-d] and treatment of α-hydroxy esters with nucleophilic fluorine sources.[6a,e,7] With these traditional methods there are few reports of the asymmetric synthesis of α-fluoro aldehydes and ketones. For example, a tertiary α-fluoro aldehyde (91% ee) was prepared in a series of steps from an enzyme resolved monoethyl 2-fluoro-2-methylmalonate.[8] α-Fluoro ketones (96-97% ee) were prepared in good yield by Kabat using Sharpless asymmetric epoxidation and ring-opening of the chiral allene oxide with TBAF.[9] Alternatively, these compounds can be prepared via the electrophilic fluorination of chiral and prochiral enolates with electrophilic fluorinating reagents such as *N*-fluorobenzenesulfonimide (**1**, NFSi)[10] and (+)-*N*-fluoro-2,10-camphorsultams **2**,[11] respectively. Indeed

Scheme 1



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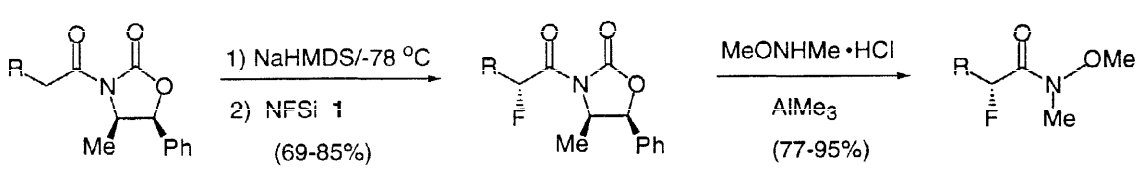
Enders et al. described the synthesis of enantiomeric pure α-fluoro ketones (>96% ee) via the electrophilic fluorination of chiral α-silylketone enolates with NFSi **1**.[12] However, only α-methylene α–fluoro ketones, lacking unsaturated substrates, can be prepared by this method because the α-silyl group is used to direct the asymmetric introduction, and O_3 is required to remove the SAMP hydrazone auxiliary in the preparation of the α-silylketone. With (+)-**2** the ee's for the asymmetric fluorination of prochiral enolates are modest (10-76% ee).[10]

In 1992 we introduced the α-fluoro oxazolidinone carboximide **3** building blocks for the asymmetric synthesis of α-fluoro carbonyl compounds.[13] Carboximide **3** is readily prepared, with predictable stereochemistry, via the electrophilic fluorination of oxazolidinone carboximide enolates with reagents such as **1** or *N*-fluoro-*o*-benzenesulfinimide (NFOBS).[13] This building block has been employed in highly efficient asymmetric syntheses of β-fluorohydrins,[13] α-fluoro esters,[13,14] tertiary α-fluoro aldehydes[15] and fluorosugars.[16] Employing **3**, we recently described the first enantioselective synthesis of an epimerizable α-fluoro aldehyde.[16a] Utilizing **3** and its corresponding Weinreb *N*-methoxy-*N*-methyl amides,[17] we described a new method for the asymmetric synthesis of α-fluoro ketones which avoids the limitations of the Enders method.

The requisite α-fluoro oxazolidinone carboximides **3a-c** were prepared as previously described by addition of 1.0 equivalents (typically 1.54 mmol) of the sodium enolates of **4a-c**,[18] prepared using 1.1 equivalents of sodium bis(trimethylsilyl)amide (NaHMDS), to 1.3 equivalents of **1** at -78 °C in THF (Scheme 2).[13] Addition of **1** to the enolate resulted in reduced yields as a consequence of enolate quenching by the acidic α-fluoro proton in the product (Table 1: compare entries 1 and 2).[19] It is important to note that the de's for **3** are were generally better with **1** than the NFOBS reagent.[13] Products were isolated by flash chromatography and the de's were determined by ^{19}F and ^{1}H NMR spectroscopy. Crystallization (EtOAc/*n*-hexane) improved the de's to >97%. These results are summarized in Table 1.

We next converted the α-fluoro carboximides **3a-c** into the α-fluoro *N*-methoxy-*N*-methylamides **5** via the transamination procedure developed by Weinreb[20] and applied by Evans to oxazolidinone carboximides.[21] Thus the aluminum amide reagent was prepared at rt by treatment of 3.0 equivalents of *N*,*O*-dimethylhydroxyamine hydrochloride (5.28 mmol) with 3.0 equivalents of trimethylaluminum in CH_2Cl_2. After stirring for 15 min. at rt and cooling to 0 °C, 1.0 equivalent of the appropriate carboximide **3** was added. The yellow solution was stirred for 2-3 h at 0 °C until completion, as monitored by TLC. After quenching with 1 % HCl the α-fluoro *N*-methoxy-*N*-methylamides **5** were isolated as oils in 77-95% yield by flash chromatography (Table 1). The enantiomeric purity was assumed to be >97% based on their conversion to the α-fluoro ketones (vide infra).

Scheme 2



4a: R = Ph
b: R = Me
c: CH_2=CH-

(*R*)-**3**

(*R*)-**5**

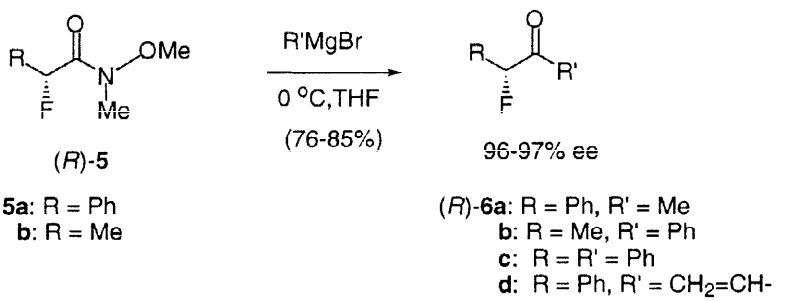
Table 1: Enantioselective Synthesis of α-Fluoro *N*-Methoxy-*N*-methylamides (*R*)-**5**.

entry	**4** (R =)	(*R*)-**3** % Yield[a] (% de)[b]		(*R*)-**5** % Yield (% ee)[c]
1	**4a**, R = Ph	85	(>97)	77 (>97)
2	**4a**, R = Ph	64[d]	(>97)	
3	**4b**, R = Me	77	(86) [>97][e]	80 (>97)
4	**4c**, R = CH_2=CH-	69	(84) [>97][e]	95 (>97)

a) Isolated yields. b) Determined by ^{19}F NMR. c) Assumed to be >97% based on conversion to the ketone. d) Addition of NFSi **1** to the enolate. e) After crystallization.

The α-fluoro ketones (*R*)-**6** were prepared in 75-85% yield by treatment of the α-fluoro *N*-methoxy-*N*-methylamides **5** with 1.1 equivalents of the appropriate Grignard reagent (R'MgBr, typically 0.28 mmol) at 0 °C in THF for 10-15 min. (Scheme 3). Addition of PhMgBr to **5c** resulted in a complex mixture of products. After quenching with sat. NH_4Cl solution the ketones **6** were isolated by preparative TLC. The enantiomeric purity of **6** were judged to be >96% using ^{19}F NMR and the chiral shift reagent Eu(hfc)$_3$. In contrast to most α-fluoro aldehydes, which decompose on standing and can not be purified by chromatography,[16a,22] α-fluoro ketones (*R*)-**6** are stable, giving satisfactory elemental analysis and showing no deterioration on storage for several months at rt. These results are summarized in Table 2.

Scheme 3



(*R*)-**5**

5a: R = Ph
b: R = Me

96-97% ee

(*R*)-**6a**: R = Ph, R' = Me
b: R = Me, R' = Ph
c: R = R' = Ph
d: R = Ph, R' = CH_2=CH-

Table 2: Asymmetric Synthesis of α-Fluoro Ketones (*R*)-**6** in THF at 0 °C

entry	Ketone **6** R	R'	% Yield[a]	% ee[b]	$[\alpha]^{20}_D$ (*c*, $CHCl_3$)		δ ^{19}F (J in Hz)[c]
1	Ph	Me	77	>97	-20.59	(0.51)	-183.2 d (52)
2	Me	Ph[d]	80	>97	+2.91	(1.2)	-181.8 m
3	Ph	Ph[e]	85	96	-95.10	(0.53)	-176.0 d (51.5)
4	Ph	$CH=CH_2$-	76	>97	-22.13	(0.80)	-184 d (51.5)

a) Isolated yields. b) Ee's were determined by ^{19}F NMR using Eu(hfc)$_3$ and comparison with racemic **6**. c) Referenced to $CFCl_3$. d) See reference 10a. e) See reference 6e.

In summary, a new highly efficient enantioselective synthesis of α-fluoro ketones **6** is reported which improves and complements earlier methods.

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References and Notes

1. For reviews on biologically active organofluorine compounds see: a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, John Wiley & Sons, New York, 1991. b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. c) *Biomedical Frontiers of Fluorine Chemistry,* Ojima, I, McCarthy, J. R.; Welch, J. T. Eds., ACS Symposium Series 639, American Chemical Society: Washington D. C., 1996. d) *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series, Vol. 456; American Chemical Society: Washington, DC, 1991. e) O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc. Chem. Commun.* **1997**, 645.
2. For recent reviews on selective fluorination see: a) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505. b) Mascaretti, O. A. *Aldrichimica Acta* **1993**, *26*, 47.
3. For reviews on the synthesis and properties of chiral organofluorine compounds see: Bravo, P., Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661. See also: Yamazaki, T.; Welch, J. T.; Plummer, J. S.; Gimi, R. H. *Tetrahedron Lett.* **1991**, *32*, 4267.
4. For a review of α-fluorocarbonyl compounds see: Rozen, S. Filler, R. *Tetrahedron*, **1985**, *41*, 1111.
5. Kalaritis, P.; Regenye, R. W. *Org. Syntheses* **1990**, *69*, 10. Kalaritis, P.; Regenye, R. W.; Partridge, J. J.; Coffen, D. L. *J. Org. Chem.* **1990**, *55*, 812.
6. a) Lowe, G. Potter, B. V. L. *J. Chem. Soc. J. C. S. Perkin Trans I*, **1980**, 2029 and references cited therein. b) Olah, G. A., Welch, J. *Synthesis* **1974**, 652. c) Faustini, F.; De Munari, S.; Panzeri, A.; Villa, V.; Gandolfi, C. A. *Tetrahedron Lett.* **1981**, *22*, 4533. d) Olah, G. A.; Surya, G. K. S.; Chao, Y. L. *Helv. Chim. Acta* **1981**, *64*, 2528. e) Cantrell, G. L.; Filler, R. *J. Fluorine Chem.* **1985**, *27*, 35.
7. a) Focella, A.; Bizzarro, F.; Exon, C. *Syn. Commun.* **1991**, *21*, 2165. b) Shiozaki, M.; Kobayashi, Y.; Arai, M. *Tetrahedron* **1991**, *47*, 7021. c) Watnanabe, S.; Fujita, T.; Usui, Y. *J. Fluorine Chem.* **1986**, *31*, 247. d) Hamman, S.; Barrelle, M.; Tetaz, F.; Beguin, C. G. *J. Fluorine Chem.* **1987**, *32*, 85. e) Fritz-Langhals, E.; Schutz, G. *Tetrahedron Lett.* **1993**, *34*, 293.
8. Yamazaki, T.; Yamamoto, T.; Kitazume, T. *J. Org. Chem.* **1989**, *54*, 83.
9. Kabat, M. M. *Tetrahedron: Asymmetry*, **1993**, *4*, 1417.
10. a) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730. b) Differding, E.; Ofner, H. *Synlett.* **1991**, 187.
11. Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273.
12. Enders, D.; Potthoff, M.; Raabe, G.; Runsink, J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2362.
13. Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153.
14. Siddiqui, M. A.; Marquez, V. E.; Driscoll, J. S.; Barchi, J. J., Jr. *Tetrahedron Lett.* **1994**, *35*, 3263.
15. Less, S. L.; Leadlay, P. F.; Dutton, C. J.; Stauton, J. *Tetrahedron Lett.* **1996**, *37*, 3519.
16. a) Davis, F. A.; Kasu, P. V. N.; Sundarababu, G.; Qi, H. *J. Org. Chem.* **1997**, *62*, 7546. b) Davis, F. A.; Qi, H. *Tetrahedron Lett.* **1996**, *37*, 4345.
17. For a review on Weinreb amides see: Sibi, M. *Org. Prep. Procedures Int.* **1993**, *25*, 15.
18. a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. b) Evans, D. A. Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. c) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
19. Decomposition results on generation of the enolates of α-fluoro oxazolidinone carboximides **3**.
20. a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
21. Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067.
22. For examples of racemic α-fluoro ketones see: a) Purrington, S. T.; Lazaridis, N. V.; Bumgardner, C. L. *Tetrahedron Lett.* **1986**, *27*, 2715. b) Patrick, T. B.; Hosseini, S.; Bains, S. *Tetrahedron Lett.* **1990**, *31*, 179.
23. Selected properties of **3** and **5**: (+)-**3b**, mp 70-74 °C, $[\alpha]^{20}_D$ 61.16 (*c* 1.2, $CHCl_3$); (*R*)-(-)-**5a**, oil, $[\alpha]^{20}_D$ -104.8 (*c* 1.1, $CHCl_3$); (*R*)-(+)-**5b**, oil, $[\alpha]^{20}_D$ 20.98 (*c* 1.12, $CHCl_3$); (*R*)-(-)-**5c**, oil, $[\alpha]^{20}_D$ -26.79 (c 1.1, $CHCl_3$).